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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,538	03/07/2002	Deb K. Chatterjee	IVGN 300	8240

65482 7590 06/10/2008

INVITROGEN CORPORATION
C/O INTELLEVATE
P.O. BOX 52050
MINNEAPOLIS, MN 55402

EXAMINER	
PROUTY, REBECCA E	
ART UNIT	**PAPER NUMBER**
1652	

MAIL DATE	DELIVERY MODE
06/10/2008	PAPER

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/091,538
Filing Date: March 07, 2002
Appellant(s): CHATTERJEE ET AL.

Elizabeth A. Orr
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 2/1/08 and supplemental brief filed 3/12/08 appealing from the Office action mailed 5/3/07.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct. However, it should be noted that the amendment filed 2/20/07 discussed by appellants was not an after-final amendment.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,664,379	Kudlicki et al.	12/2003
WO 00/55353	Swartz et al.	9/2000

Pratt, J. M. "Coupled Transcription-Translation In Prokaryotic Cell-Free Systems", Transcription and Translation: a Practical Approach (B.D. Hanes et al. eds.): 179-209, (1984).

Yu, D., et at., "An efficient recombination system for chromosome engineering in *Escherichia coli*," PNAS 97:5978-5983, (May 2000).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1, 16, 17, 27, 28, 30, 35, 39, 41, 42, 51-60, 85, 88, 91, and 94 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Pratt (1984) in view of Yu et al. (Reference AR14 of applicant's IDS of 7/02).

Pratt. teach an *E. coli* coupled transcription/translation system (ITT) comprising an extract of an *E. coli* strain having a mutation in the *recB* gene (see pages 200-201) such that the extract exhibits a lack of the RecBCD exonuclease (also called exonuclease V) and a template DNA as well as several energy sources (i.e., ATP, GTP, and PEP). This ITT system is disclosed as particularly useful for linear DNA templates as these type of

templates are particularly susceptible to degradation by the RecBCD exonuclease. Pratt however teach that these strains produce systems with high levels of background synthesis due to large amounts of contaminating chromosomal fragments or require an extended pre-incubation step (see pages 200-201). Pratt et al. also teach *E. coli* coupled transcription/translation systems comprising an extract of *E. coli* strain MRE600, which strain has a mutation in the major RNase of *E. coli* (i.e., RNase E) but is wild type for the production of the RecBCD exonuclease which system is disclosed as preferred for all other applications which do not use linear DNA templates (see page 183).

Yu et al. teach that mutant *recBCD* strains have been used to prevent the rapid degradation of linear DNAs but that such strains lacking the RecBCD exonuclease are extremely poor growing. Yu et al. teach that one can alternatively inhibit the RecBCD exonuclease using the lambda phage Gam protein (see page 5578).

While Pratt clearly teaches a different use of mutant strains lacking the *E.coli* recBCD exonuclease than that of Yu et al., in both instances, the lack of recBCD exonuclease activity has substantial benefits for particular applications but has substantial shortcomings when compared to wild type strains. As such, both Pratt and Yu et al. teach that the use of a mutant

strain lacking the *E.coli* recBCD exonuclease has both desirable benefits as well as substantial shortcomings for a desired method. Yu et al. teach that the solution to this is to replace the use of the mutant strain with a wild type strain in combination with the λ Gam protein which is an inhibitor of the recBCD protein. A skilled artisan would have found it obvious to combine Pratt and Yu et al. as the problem to be solved is the same for both types of systems. Therefore, it would have been obvious to one of ordinary skill in the art to replace the use of the *recB E. coli* strain used by Pratt et al. with a wild type *E. coli* strain (such as the MRE600 strain disclosed by Pratt as being the preferred strain for preparation of the S30) and to include the lambda phage Gam protein in the transcription/translation reaction to inhibit the degradation of linear template DNAs.

Claims 86, 87, 89, 90, 92, 93, 95, and 96 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Pratt (1984) in view of Yu et al. (Reference AR14 of applicant's IDS) as applied to claims 1, 16, 17, 27, 28, 30, 35, 39, 41, 42, 51-60, 85, 88, 91, and 94 above, and further in view of Swartz et al. (WO 00/55353).

Pratt and Yu et al. are discussed above but do not specifically teach using 2 different energy sources selected

from the group consisting of pyruvate, PEP, carbomyl phosphate, acetyl phosphate, creatine phosphate, phosphopyruvate, glyceraldehydes-3-phosphate and glucose-6-phosphate or particularly PEP and acetyl phosphate in the ITT system described.

Swartz et al. teach the alteration of the energy generation system of synthetic systems including the ITT systems described by Pratt et al. by replacing the PEP regeneration system with a system which regenerates acetyl phosphate or systems which include small amounts of secondary energy sources (e.g. acetyl phosphate, PEP and creatine phosphate in combination with pyruvate and pyruvate oxidase (see page 6). As such it would have been obvious to one of ordinary skill in the art to substitute the energy generating systems of Pratt et al. with the systems disclosed by Swartz et al.

Claims 61, 62, 69, 70, 77, and 78 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Pratt (1984) in view of Yu et al. (Reference AR14 of applicant's IDS) as applied to claims 1, 16, 17, 27, 28, 30, 35, 39, 41, 42, 51-60, 85, 88, 91, and 94 above, and further in view of Kudlicki et al. (US Patent 6664,379).

Pratt and Yu et al. are discussed above and teach the use of extracts of the *E. coli* strain MRE600 in which the major

RNase activity of *E. coli* is deleted but do not specifically teach using an extract of an *E. coli* strain deleted for one or more DNAses.

Kudlicki et al. teach the inhibition of multiple RNases and DNases during synthetic reactions including ITT systems.

As Kudlicki et al teach the elimination of DNase activity as well as RNase activity during an ITT reaction is useful and as the genome of *E. coli* is known, it would have been obvious to one of ordinary skill in the art to delete the genes encoding one of more DNases of *E. coli* to reduce the DNase activity of the ITT extract.

(10) Response to Argument

(A) Rejection of Claims 1, 16, 17, 27, 28, 30, 35, 39, 41, 42, 51-60, 85, 88, 91, and 94 under 35 U.S.C. 103(a) over Pratt (1984) in view of Yu et al.

Appellants argue that the cited references do not disclose each and every claim limitation as independent claims 1, 41, and 51 recite an *in vitro* synthesis system, a kit, and a composition that include an *E. coli* cell extract, in which the *E. coli* cell used to make the extract has a mutation that reduces the activity of a nuclease, in which the cell does not express Gam, and in which the extract is modified by the addition of Gam protein. Neither Pratt nor Yu et al. disclose an extract and Gam

protein as recited in amended claims 1, 41, and 51. However, this is not in fact a true statement. First it should be noted that the instant rejection is a 103 rejection and NOT a 102 rejection such that all elements of the claim need not be present in either of Pratt or Yu et al. alone but only in the combination thereof. All elements of the recited claims are in fact present in the combined disclosures of Pratt and Yu et al. Pratt clearly teach an *E. coli* cell used to make an ITT extract and ITT systems including said extract which has a mutation that reduces the activity of a nuclease, in which the cell does not express Gam (i.e., *E. coli* MRE600). This strain of *E. coli* includes a mutation in the major RNase of *E. coli* (i.e., RNase E) and is wild type for production of the *RecBCD* exonuclease but is not infected with the lambda phage and thus does not express the lambda Gam protein. Yu et al. teach the lambda Gam protein and teach its addition to an *E. coli* cell which is wild type for production of the *RecBCD* exonuclease in order to inhibit the activity of the *RecBCD* exonuclease.

Appellants argue that neither Pratt or Yu et al., alone or in combination, suggest or provide motivation for making of an *in vitro* synthesis system with a cell extract that includes added Gam protein. However, while neither Pratt nor Yu et al. may make an explicit statement which suggests adding the Gam

protein to an ITT extract, the rejection clearly did provide sufficient motivation. As discussed above, both Pratt and Yu et al. teach that the use of a mutant strain lacking the *E.coli* recBCD exonuclease has both desirable benefits as well as substantial shortcomings for a desired method. While Pratt clearly teaches a different use of mutant strains lacking the *E.coli* recBCD exonuclease than that of Yu et al., in both instances, the lack of recBCD exonuclease activity has substantial benefits for the particular application but also has substantial shortcomings when compared to wild type strains. Yu et al. teach that the solution to this is to replace the use of the mutant strain with a wild type strain in combination with the λ Gam protein which is an inhibitor of the recBCD protein. A skilled artisan would have found it obvious to combine Pratt and Yu et al. as the problem to be solved is the same for both types of systems. Appellants argue that Pratt does not suggest solving the problems resulting from use of a recB mutant strain by using a recBCD inhibitor but instead by using the methods of Zubay or Gold and Schweiger. However, the rejection is not made over Pratt alone but instead over the combination of Pratt and Yu et al. Yu et al. clearly teach a different approach to solving the inherent problems of use of recB mutant *E. coli* than that taught by Zubay or Gold and Schweiger et al. Furthermore,

as the use of a protein inhibitor of recBCD as taught by Yu et al. would be substantially simpler than the methods of Zubay or Gold and Schweiger et al., requiring merely the addition of a protein to the ITT extract, a skilled artisan would clearly have been motivated to use the approach taught by Yu et al. Appellants argue that neither Pratt nor Yu et al. disclose ITT extracts in which the extract is modified by the addition of Gam protein. Appellants argue that Yu et al. do not teach inhibition of a nuclease by addition of a protein to the cell extract but rather, Yu et al. teach expression of the Gam gene within cells that also express RecBCD nuclease. However, this is not persuasive as appellants are arguing distinctions in the method of preparation of the claimed extract and not a distinction in the extract itself. Appellants are reminded that their claims recite products and not a process of making the product. There would be no real distinction between a cell extract made by transforming a cell with a heterologous gene, culturing the cell so as to express the gene and making an extract and an extract made by culturing an otherwise similar cell which is not transformed, making a cell extract and then adding an amount of the same protein produced by the heterologous gene to the cell extract. In each case the result is a cell extract which includes all proteins etc. produced by

the cell before modification (i.e., transformation or exogenous addition) as well as an amount of the heterologous protein also. The only actual difference between these products would be in the genetic material of the cell from which the extract is made (which in the case of expression within the cell would include the gene encoding Gam while this gene would not be present in the case of exogenous addition) but the genetic material of the cell from which an ITT extract is prepared in no way participates in an ITT reaction. Expression of the Gam gene within cells is a means of adding Gam protein to the cells. It may be an indirect method of addition, but it still results in a cell extract which includes a protein that was not there previously. In fact even appellants own specification indicates the equivalence of exogenous addition of an inhibitor to a cell extract and expressing the inhibitor within the cell and then preparing an extract of the cell. Paragraph [0045] on page 15 of the specification states:

> Inhibitors can be used or included in the systems of the invention by any known method. For example, inhibitors may be added to the system before, during or after introduction of the nucleic acid template. Inhibitors can also be transcribed or expressed in a cell used to prepare the extract or transcribed or expressed during the protein synthesis reaction.

As such appellants arguments suggesting that expression of the Gam protein within the cell of Yu et al. is not addition of the Gam protein to the cells of Yu et al. are not persuasive.

Appellants further argue that one of ordinary skill in the art would not have a reasonable expectation of success in producing an *in vitro* synthesis system by adding Gam protein to an *E. coli* extract to produce an *in vitro* synthesis system as at the time the invention was made, it was not known whether addition of Gam protein to an *E. coli* cell extract would protect linear DNA molecules from degradation, if the use of Gam protein in an *in vitro* synthesis system would adequately reduce or eliminate recBCD activity, or whether it would interfere with transcription and/or translation. However, Yu et al. clearly demonstrate that the addition of Gam was successful to inhibit the degradation of linear DNAs in the recombination system Yu et al. was utilizing such that a skilled artisan would expect it to function similarly in an ITT system as both are systems which include the entire cellular mix of *E. coli* proteins and applicants have advanced no reason for a skilled artisan to believe that addition of the Gam protein (whether by exogenous addition or by expression in the cell prior to preparation of the extract) would interfere with transcription and/or translation. Since the function of the Gam protein is to

inhibit the RecBCD nuclease which is a protein not known to be involved in the processes of transcription and translation, a skilled artisan would not expect addition of Gam to be detrimental to these processes. Appellants are reminded that obviousness does not require an absolute certainty of success, but only a reasonable expectation thereof.

(B) Rejection of Claims 86, 87, 89, 90, 92, 93, 95, and 96 under 35 U.S.C. 103(a) over Pratt (1984) in view of Yu et al. and further in view of Swartz et al. (WO 00/55353).

Appellants have not presented any arguments specifically traversing this rejection but instead rely upon the traversal provided for the rejection of claims 1, 16, 17, 27, 28, 30, 35, 39, 41, 42, 51-60, 85, 88, 91, and 94 over Pratt in view of Yu et al. discussed above. Therefore, this rejection is maintained for the reasons presented above.

(C) Rejection of Claims 61, 62, 69, 70, 77, and 78 under 35 U.S.C. 103(a) over Pratt (1984) in view of Yu et al. and further in view of Kudlicki et al. (US Patent 6664,379.

Appellants have not presented any arguments specifically traversing this rejection but instead rely upon the traversal provided for the rejection of claims 1, 16, 17, 27, 28, 30, 35, 39, 41, 42, 51-60, 85, 88, 91, and 94 over Pratt in view of Yu

et al. discussed above. Therefore, this rejection is maintained for the reasons presented above.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Rebecca E. Prouty/
Primary Examiner,
Art Unit 1652

Conferees:

/Robert A. Wax/
Robert A. Wax
TQAS Appeals Specialist
Technology Center 1600

/Nashaat T. Nashed/
Supervisory Patent Examiner,
Art Unit 1652